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#4 (NE)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Barberá-Guillem & Nelson

Attny Docket: **B-29**

Application No. 09/643,595 Examiner: J. Roark, Ph.D.

Filed: 22 August 2000 Art Unit 1644

For: Methods and compositions for immunotherapy of B cell involvement in promotion of a disease condition comprising multiple sclerosis

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action dated 05 July 2001 (hereinafter referred to as "OA"), Paper No. 3, please be advised as follows.

The Examiner has required a more descriptive title of the invention (OA, item 3). In response, the Applicants have amended the title to "Methods for immunotherapy of an immune response which promotes a disease condition comprising multiple sclerosis". In amending the title, the Applicants submit Exhibit 1 showing both a corresponding replacement paragraph/section, and a marked-up version, in accordance with 37 CFR §1.111. The Examiner is respectfully directed to Exhibit 1.

The Examiner has objected to claims 1-17 because of the informality of use of the abbreviation "MS" for "multiple sclerosis" (OA, item 6). Claims 1, 6, and 10 have been amended to spell out multiple sclerosis in its first use, followed by the abbreviation, and subsequent use of the abbreviation in dependent claims, the abbreviation being well known to those skilled in the art. This form of claim complies with **MPEP 608.01(m)**, as it is

recognized by those of ordinary skill in the art (as well as those not skilled in the art) that the terms "multiple sclerosis" and "MS" are interchangeable. The Applicants respectfully traverse the objection with respect to claim 14. Claim 14 complies with **MPEP 608.01(m)** (**see also**, the Examiner's suggested language in OA, item 10). With respect to claim 14 as filed, and amended claims 1, 6, and 10, the meaning of the abbreviation MS as a term in the claims is apparent from the descriptive portion of the specification, and has a meaning which is clear to one skilled in the art, in accordance with **MPEP 608.01(o)**.

The Examiner has objected to claims 2, 7, 11 and 15 because of the informality of use of lowercase "+" as indicating positive expression of that particular cell surface marker (OA, item 7). Claims 2, 7, 11, and 15 have been amended, in accordance with the Examiner's suggestions, to indicate each "+" as a superscript, in indicating positive expression of the respective cell surface marker. The Applicants are appreciative of the claim language suggested by the Examiner.

The Examiner has objected to claim 4 because of the informality concerning the Markush language used (OA, item 8). Claim 4 has been amended in accordance with the Examiner's suggestions. The Applicants are appreciative of the claim language suggested by the Examiner.

The Examiner has objected to claim 6 because of the informalities of (a) a duplicative use of the term "for reducing"; and (b) and the use of the phrase "which the composition" instead of "wherein the composition" (OA, item 9). Claim 6 has been amended in accordance with the Examiner's suggestions. The Applicants are appreciative of the claim language suggested by the Examiner.

The Examiner has objected to claim 14 because of the informality that the use of Markush language is confusing (OA, item 10). Claim 14 has been amended in accordance with the Examiner's suggestions. The Applicants are appreciative of the claim language suggested by the Examiner.

In amending claims 1, 2, 4, 6, 7, 10, 11, 14, and 15, the Applicants submit Exhibit 2 showing both a corresponding replacement paragraph/section, and a marked-up version, in accordance with 37 CFR §1.111. The Examiner is respectfully directed to Exhibit 1. It is noted that the amendments to claims 1, 2, 4, 6, 7, 10, 11, 14, and 15, as specified above, 10-13, were made to more distinctly claim the present invention for informalities in view of the Examiner's objections while preserving the scope of the claims, and were not amended for the purpose of overcoming prior art. This point is made to preserve in the record the scope of the claims under an equivalency analysis.

Rejection of claims 2, 5, 7, 9, 11, 13-15, and 17 under 35 USC §112

Reconsideration of the rejection of claims 2, 5, 7, 9, 11, 13-15, and 17 as being indefinite under §112, second paragraph is respectfully requested for the following reasons.
Claims 2, 7, 11, and 15 have been amended to more particularly point out and distinctly claim the invention recited, and in accordance with the Examiner's suggestions for a proper Markush format.
Claims 5, 9, 13, and 17 have been amended to more particularly point out and distinctly claim the invention recited, and in accordance with the Examiner's suggestions for a proper Markush format.
Claim 14 has been amended, in accordance with the Examiner's suggestions, to include the step of administering to the individual a composition, as also recited in original claims 1, 6, and 10.

In amending claims 2, 5, 7, 9, 11, 13-15, and 17, the Applicants submit Exhibit 1 showing both a corresponding replacement paragraph/section, and a marked-up version, in accordance with 37 CFR §1.111. The Examiner is respectfully directed to Exhibit 2. The Applicants are appreciative of the claim language

suggested by the Examiner for the amendments, and which has been used in making these amendments. Support for the amendments can be found throughout the specification as filed, and in particular on page 5, lines 4-7, page 9, lines 19-27 and in referring to Table 2, and page 10, lines 4-9. In view of the amendments, the Applicants respectfully request withdrawal of the rejection of claims 2, 5, 7, 9, 11, 13-15, and 17 within the meaning of §112, second paragraph. It is noted that the amendments to claims 2, 5, 7, 9, 11, 13-15, and 17 were made to more distinctly claim the present invention for §112 purposes in view of the Examiner's rejections while preserving the scope of the claims, and were not amended for the purpose of overcoming prior art. This point is made to preserve in the record the scope of the claims under an equivalency analysis.

Rejection of claims 1-2, 4-5, 10-11, 13-15 and 17 under §102(a)

Reconsideration of the rejection of claims 1-2, 4-5, 10-11, 13-15, and 17 under §102(a) as being anticipated by Bhat et al. is respectfully requested for the following reasons.

1. The cited reference does not identically describe the claimed invention

As the Examiner is aware:

> "Rejections under 35 USC 102 are proper only when the claimed subject matter is identically disclosed or described in the prior art...(case citations). In other words, to constitute an anticipation, all material elements recited in a claim must be found in one unit of prior art" *In re Marshall*, 198 USPQ, 344, 346 (CCPA, 1978). *See* also, *Acoustiflex Corp. v. Owens-Corning Fiberglass Corp.* 223 USPQ 12,13 (N.D. Illinois, 1988).

Thus, "the law requires us to determine whether the invention has been ***identically*** described, *not* whether it has been ***logically*** described by the reference" (*In re Arkley, Eardley and Long* 172 USPQ 524, 528).

Bhat et al. teach the following (1st paragraph of Background).

[''Point One''] ''Other mechanisms may be operative in the process where a lymphoid cell attacks an endogenous epitope. These autoimmune diseases can be extremely destructive, as evidenced by diabetes, rheumatoid arthritis, neuronal diseases, such as multiple sclerosis, and the like.''

[''Point Two''] ''While in many cases, the disease is associated with T-cell attack, in some of the diseases, there may be a B cell component, and in other diseases, such as rheumatoid arthritis and lupus nephritis, the primary mediator may be B cells''.

To those skilled in the art, Point One teaches that when a lymphoid cell attacks an endogenous epitope (lymphoid cells known to attack an endogenous epitope are known by those skilled in the art to be limited to cytolytic T cells, and NK cells), an extremely destructive autoimmune disease can result, as evidenced by diabetes, rheumatoid arthritis, neuronal diseases, such as multiple sclerosis, and the like. Point Two teaches that in some of the diseases in which there is a T cell attack (**but does not teach what diseases; i.e., does not distinguish which diseases**) there may be a B cell component; and in diseases such as rheumatoid arthritis and lupus nephritis, the primary mediator may be B cells. Thus, while the Applicants agree with the Examiner in that Bhat et al. teach that MS is an autoimmune disease (OA, p.4, item 14, line 7), the Applicants respectfully disagree with the Examiner's conclusion that Bhat et al. teaches that there is a B cell component which contributes to pathogenesis of MS, and therefore, that Bhat et al. teaches that reducing B cells in individuals with MS would reduce the inflammation underlying the clinical manifestations of MS (OA, p.4, item 14, line 8-13).

Additionally, it is respectfully pointed out to the Examiner that all of claims 1-2, 4-5, 10-11, 13-15, and 17 recite reduction or treatment of a pro-MS immune response, an element of the claimed subject matter. A pro-MS immune response, a novel discovery of the Applicants, is defined in the specification (for purposes of the specification and claims) on pages 15 and 16 as a specific humoral immune response (e.g., as characterized by the inducing epitope). Thus, not only does the Bhat et al. reference fail to describe B cells as a pathogenic component of MS, it also fail to describe a pro-MS immune response. As an analogy, the Patent Office has recognized the distinction (with respect to

§102, and §103) between the prior art (such as Bhat et al. and Anderson et al.) from claims reciting a method for reducing a pro-tumor immune response (Patent No. 6,224,866 to the present assignee; a copy of which is attached in Exhibit 2 for the Examiner's convenience). A proper rejection under §102 requires that the cited reference identically describe or disclose the claimed invention (see also, **MPEP 2131-** ''to anticipate a claim, the reference must teach each and every element of the claim''). A comparison of the subject matter of the Bhat et al. reference with the subject matter of claims 1-2, 4-5, 10-11, 13-15, and 17 of the present application shows that the Bhat et al. reference does not identically disclose or describe the claimed subject matter of the present invention, and thus is not a proper §102 reference. **MPEP 706.02(a)**.

In view of the above considerations (e.g., the cited reference does not identically describe the claimed invention) and legal precedence, it is clear that the Bhat et al. reference is not prior art within the meaning of §102(a). Therefore, reconsideration of the rejection of claims 1-2, 4-5, 10-11, 13-15, and 17 under §102(a) is respectfully requested.

Rejection of claims 1-17 under §103(a)

Reconsideration of the rejection of claims 1-17 under §103(a) as being obvious in view of Turk et al. (U.S. Pat. No. 5,958,409) and Genain et al. (*J. Clin. Invest.* 1995, 96:2966-2974) and further in view of Anderson et al. (U.S. Pat. No. 5,776,456) is respectfully requested for the following reasons; the reasons being enumerated within the meaning of §103 according to legal precedence, which is binding on both the Applicants and the Patent Office, and such precedence is summarized here to be of record in this case.

In brief, the basis of the Examiner's §103(a) rejection appears to be that: (a) Turk et al. teaches (i) a method for

treating MS by administering an affinity ligand that is a chimeric antibody, and (ii) that serum antibodies are important in producing the CNS pathology observed in MS; (b) Genain et al. teach that antibodies initiate the demyelination observed in MS; (c) Anderson teaches use of a chimeric anti-CD20 antibody to deplete B cells *in vivo*; and (d) therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the references and have a reasonable expectation of success in a method of depleting B cells that "*initiate*" pathology underlying MS. Further, the combination of references make it obvious that the B cell populations involved in a pro-MS immune response express CD20 and therefore are susceptible to depletion with chimeric anti-CD20 antibody.

A. The Applicants respectfully submit that it is well established law (see, e.g., §103(a); *Graham v. John Deere Co.* 383 U.S. 1, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); *Robotic Vision Systems, Inc. v. View Engineering, Inc.*, 189 F.3d 1370 (Fed. Cir. 1999)) and patent prosecution practice (**MPEP 2141.01**- Scope & Content of Prior Art, (c) *Content of the prior art is determined at the time the invention was made to avoid hindsight*), that obviousness is determined by reference to the level of skill of one having ordinary skill in or knowledge of the art at the time the invention was made. To establish the level of ordinary skill or knowledge in the art at the time the invention was made, the Applicants submit herewith, in Exhibit 3, Rudick et al. (1997, *The New England Journal of Medicine*, 337:1604-1611), Hjelmström et al. (1998, *J. Immunology*, 161:4480-4483), Wolf et al. (1996, *J. Exp. Med.* 184:2271-2278), and Karni et al. (1999, *Arch. Neurol.* 56:311-315).

(A) The Rudick et al. reference summarizes the art of treatment of MS at the time of the invention was made as well as the accepted view of the pathogenesis of MS at the time of the invention. In that regard, pathogenesis, and known targets for

therapy, as reviewed in FIG. 1 of and described in the text by Rudick et al. comprise: autoreactive T-cells (1); preventing T cells from crossing blood-brain barrier (2); antigen-presenting cells which present antigen to T cells (e.g., dendritic cells or CNS-equivalent)(3); and immunosuppressive cytokines (4). B cells, and a pro-MS immune response, are absent from this model of pathogenesis reviewed by Rudick et al. and as understood by those skilled in the art at the time the invention was made. Additionally, there is a lack of teaching, suggestion or motivation to one of ordinary skill and knowledge in the art to treat an individual to reduce a pro-MS immune by administering a composition comprising affinity ligand in an amount effective to deplete B cells.

(b) The rodent model of experimental allergic encephalomyelitis (EAE) is accepted by those skilled in the art as the standard experimental model for MS (see, e.g., Introduction of Genain et al., of record). The Hjelmström et al. reference and the Wolf et al. reference describe that, at the time the invention was made, it was known by those skilled in the art that B cell-deficient mice develop EAE with demyelination. Thus, it is clear to one skilled in the art at the time the invention was made that: antibodies do not initiate the demyelination observed in MS (contrary to the Examiner's opinion of the teachings of Genain et al.; see, OA, p. 5, line 17); that B cells do not initiate demyelination observed in MS, as demyelination occurs in the absence of B cells (contrary to the Examiner's opinion of the teachings of Genain et al.; see, OA, p.5, line 24); that B cells do not produce autoantibodies that "*initiate*" the pathology of MS (e.g., inflammatory lesions and demyelination; see Abstract of Hjelmström et al.), since the pathology can be initiated in the absence of B cells (contrary to the Examiner's opinion of the teachings of Genain et al.; see, OA, p.5, lines 29-31). Further, from viewing the disclosure of Hjelmström et al. as a whole, one skilled in the art at the time the invention was made would conclude that the role, if any, of B cells and their products on

the pathology of MS remains unknown. For example, Hjelmström et al. conclude their publication with the following last remark:

"The elucidation of the role of B cells and their products in the regulation of inflammatory processes and clinical disease in MS and EAE will be the subject of further studies".

Likewise, in viewing the Wolf et al. reference as a whole, not only do they teach that they observe no difference in the onset or severity of the disease EAE in the absence of mature B cells, but also they also suggest that B cells may actually play a role in the recovery from the disease by functioning to shift from a Th1 response to a Th2 (recovery) response (see, e.g., p. 2276, column 2, lines 7-15). Thus, based on what was known by those skilled in the art at the time of the invention, one of ordinary skill in the art would not have a reasonable expectation of success that by depleting B cells would also reduce both the pro-MS immune response and the underlying clinical symptoms of MS (see, e.g., OA, p. 5, lines 29-33). Until a role of B cells is elucidated, in fact one skilled in the art would be directed away from depleting B cells because of their possible role in a recovery response, as proposed by Wolf et al. It is noted that those skilled in the art at the time of the invention were investigating the role, if any, of B cells in the pathogenesis of MS; but there lacked any teaching or suggestion of a specific humoral immune response that can be induced in MS which promotes the progression of MS.

Evidence of a long-felt but unsolved needs and failure of others must be considered by the Examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C 103. **MPEP 716.4**; See also *Stratoflex, Inc. v. Aeroquip Corp.* 218 USPQ 871, 879 (Fed. Cir. 1983).

The present application provides the discovery and elucidation of a role that B cells play in progression of MS (please note the Applicants did not state in the application that the pro-MS immune response "*initiated*" the pathology observed in MS, but rather "exacerbate the ongoing inflammatory process, thereby promoting progression of MS" (see, e.g., p. 5, lines 26-27; p. 6, lines 20-28).

(c) Karni et al. describe that (see, p. 311, Conclusions), at the time the invention was made, it was known by those skilled in the art that while anti-myelin oligodendrocyte glycoprotein (MOG) antibodies are present in MS (note Genain et al. disclose the existence of anti-MOG antibodies in a marmoset model of EAE):

(i) the elevated levels of such antibodies are not specific to individuals having MS (i.e., but are also present in individuals with other neurological diseases not characterized by demyelination, see, e.g., p. 312, "Patients"); and

(ii) it is unclear "whether this antibody is pathogenic in MS, or on the contrary, has a defensive role against further immune-mediated damage after myelin breakdown" (p. 311, Conclusions).

In contrast to Genain et al. which describes a marmoset model of EAE, Karni et al. describe actual patients with MS. Until a role of antibody is elucidated in the process of MS, one skilled in the art would be directed away from depleting B cells with consequent depletion of antibody because of the possible role of antibody in a defensive role against further immune-mediated damage after myelin breakdown, as suggested by Karni et al.

> Evidence of a long-felt but unsolved needs and failure of others must be considered by the Examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C 103. **MPEP 716.4**; See also *Stratoflex, Inc. v. Aeroquip Corp.* 218 USPQ 871, 879 (Fed. Cir. 1983).

The present application provides the discovery and elucidation of antibodies of a defined specificity, that when in the form of immune complexes, play a role in progression of MS.

The Applicants have met Applicants' burden to establish the level of ordinary skill and knowledge in the art at the time the invention was made, and why the combination of references cited by the Examiner would not teach, suggest, or motivate one of ordinary skill and knowledge in the art to combine or modify the combination of references with a reasonable expectation to achieve the claimed invention. The burden now shifts to the Examiner to provide evidence or a convincing line of reasoning to support a position of obviousness.

> In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select elements from the cited prior art references for combination in the manner claimed. *In re Denis Rouffet, Yannick Tanguy and Frederic Berthault*, 149 F.3d 1350,1357 (Fed. Cir. 1998).

B. In determining the question of obviousness, references may be combined; and each reference is important for what it contributes to the combination. *Sterling Aluminum Products v. Bohn Aluminum & Brass Corp.* 187 F. Supp. 879,885 (E.D. Mich., 1960), affirmed 298 F.2d 538 (6th Cir., 1962). Thus, while it is not necessary for a single reference to disclose all the limitations of a claim, the teachings of a single reference must be considered for what it fairly teaches as its contribution to the combination of references. To analyze what a reference fairly teaches as it's contribution to the combination of references, it is necessary to consider the scope and content of the prior art, and the differences between the prior art and the claims at issue. **MPEP 2141.01**- Scope & Content of Prior Art. *Graham v. John Deere Co.* 383 U.S. 1, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); *Robotic Vision Systems, Inc. v. View Engineering, Inc.*, 189 F.3d 1370 (Fed. Cir. 1999). Additionally, the Examiner is also respectfully reminded that when a reference is analyzed for what it fairly teaches as its contribution to the combination of references, and when considering the scope and content of such reference, the reference must be considered as a whole. *W.L. Gore & Associates, Inc v. Garlock*, 721 F.2d 1540,1550, 220 U.S.P.Q 303,311 (Fed. Cir. 1983), cert denied 469 U.S. 851; *Akzo N.V. v. United States Int'l Trade Comm'n*, 1 U.S.P.Q.2D 1241 (Fed. Cir. 1986).

More specifically, with regard to consideration of a reference as a whole:

> Under §103 a "patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains...." (emphasis added).

> In deciding the question of obviousness under 35 U.S.C. §103, it is not proper to pick and choose from any one reference only so much as it will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fully suggests to one of ordinary skill in the art. *State Industries, Inc. v. A.O. Smith Corp.*, 221 USPQ 958,972 (M.D. Tenn. 1983); *In re Lunford*, 357 F.2d 380,384, 148 USPQ 716,719-720 (CCPA 1966).

With a summary of the legal precedence regarding an obviousness analysis set forth above, a first step is to compare the scope and content of the prior art references cited by the Examiner with the claimed invention.

The Examiner's opinion on what each reference contributes to the combination is summarized as follows: (a) Turk et al. teaches (i) a method for treating MS by administering an affinity ligand that is a chimeric antibody, and (ii) that serum antibodies are important in producing the CNS pathology observed in MS; (b) Genain et al. teach that antibodies, products of B cells, initiate the demyelination observed in MS; (c) Anderson teaches use of a chimeric anti-CD20 antibody to deplete B cells *in vivo*; and (d) therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the references and have a reasonable expectation of success in a method of depleting B cells that "*initiate*" pathology underlying MS (se, e.g., OA, p. 5).

In determining the scope and content of each reference of the combinations of references, the Applicants respectfully disagree with the Examiner's analysis (as detailed in the OA, p. 5). With respect to the scope and content of the Genain et al. reference and what it teaches or suggests to one skilled in the art with respect to its contribution to the combination of references, the Applicants respectfully disagree with the Examiner's conclusion that:

(a) "Genain et al. teach that antibodies initiate the demyelination observed in MS" (OA, p. 5, line 17);

(A) Genain et al. teach "that B cells initiate the demyelina-

tion observed in MS" (OA, p. 5, line 24); and (c) Genain et al. teach "that B cells produce autoantibodies that initiate pathology" observed in MS (OA, p. 5, lines 29-30).

In light of what was known by those skilled in the art at the time of the invention (see, e.g., Karni et al., Hjelmström et al., and Wolf et al.), there is a lack of support for the supposition that one of ordinary skill in the art would interpret Genain et al. reference as teaching that antibodies, and B cells, initiate the demyelination observed in MS versus in the "unique demyelinating form" of EAE in the common marmoset that Genain et al. describe. First, it is respectfully pointed out that Genain et al. disclose antibody facilitation (in the presence of encephalitogenic T cells) of multiple sclerosis-like lesions in a "unique demyelinating form" of EAE in the common marmoset (Abstract, lines 4-5). As known to those skilled in the art, the rodent EAE model is the experimental animal model generally predictive of the human disease MS (see, Hellestrom et al. Abstract and Introduction). As noted by Genain et al., and in contrast to the marmoset's "unique demyleinating form" of EAE, transfer of MBP-reactive T cells in the accepted experimental animal model of MS comprising rodent EAE was sufficient to reproduce the distinctive pathologic lesions typical of MS (see, last paragraph of Introduction). Thus, the marmoset form of EAE is a fundamentally different pathological process than the rodent form of EAE.

To one skilled in the art at the time of the invention, it would appear that the marmoset's "unique demyleinating form" of EAE is also different than the pathology underlying rodent EAE and MS in humans. In fact, as evidenced by Karni et al., one skilled in the art at the time of the invention has the knowledge that elevated levels of such antibody (anti-MOG antibodies taught by Genain et al.) is not specific to human MS, but rather is present in neurological diseases in which demyelination is absent (see, e.g., Karni et al., p. 312, Patients). Further, it has

been suggested to one skilled in the art at the time of the invention that such antibodies may play a defensive role against further immune-mediated damage after myelin breakdown (see, e.g., Karni et al., and Wolf et al.). Additionally, one skilled in the art at the time of the invention would not interpret Genain et al. and its "unique demyleinating form" of EAE as teaching that B cells initiate the demyelination observed in MS, as it has been demonstrated in the art that B cell-deficient mice develop EAE with inflammatory lesions and primary demyelination characteristic of MS (see, Hjelmström et al., and Wolf et al.).

In determining the scope and content of each reference of the combinations of references, and with respect to the scope and content of the Turk et al. reference and what it teaches or suggests to one skilled in the art with respect to its contribution to the combination of references, the Applicants respectfully disagree with the Examiner's conclusion that:

> "Turk et al. also teach that although TNF-α has been implicated as an important effector molecule in MS, serum antibodies (i.e., the B cell-produced mediator of humoral immunity) are also important in producing the CNS pathology observed in MS (e.g. columns 2-3)" (OA, p. 5, lines 12-14).

The Applicants certainly agree with the Examiner that Turk et al. teach and suggest a role for TNF-α in the pathogenesis of MS. However, columns 2-3 of Turk et al. recite that multiple sclerosis is a:

> "disease associated with blood-brain barrier dysfunction, infiltration of the central nervous system by mononuclear cells (mainly macrophages and T lymphocytes, and serum products), and demyelination..."; and that TNFα, a serum product, "is a protein secreted primarily by monocytes and macrophages in response to endotoxin or other stimuli" (columns 2-3).

Since there is no mention in columns 2-3 of serum antibodies, or B cells involved in humoral immunity, the Examiner is respectfully requested to provide evidence or a convincing line of reasoning to support a position that this teaching of Turk et al. suggests to one of ordinary skill in the art that "serum

antibodies (i.e., the B cell-produced mediator of humoral immunity)" is "also important in producing the CNS pathology observed in MS" (OA, p.5, lines 13-14).

In view of the above considerations of the scope and content of the references in the cited combination, what the combination of references (Genain et al., Turk et al., and Anderson et al.) teach or suggest to one of ordinary skill in the art at the time of the invention is that:

(A) anti-MOG antibody facilitates (in the presence of encephalitogenic T cells) demyelination in a "unique demyelinating form" of EAE in the common marmoset (however, this animal model is different that the standard acceptable model of MS comprising rodent EAE, e.g., where demyelination can occur in the presence of T cells without antibody as disclosed by Genain et al.; and different than MS, where anti-MOG antibody may serve a protective function, see, e.g., Karl et al.);

(B) TNFα is a serum product which has a role in the pathogenesis of multiple sclerosis and EAE, (Turk et al., column 1, lines 41-43), and a method of treating MS comprises administering a therapeutically effective amount of anti-TNFα antibody (Turk et al., claim 1); and

(C) a method for treating B cell lymphoma is to administer a therapeutically effective amount of chimeric anti-CD20 antibody to deplete CD20-expressing malignant B cell lymphoma cells.

In contrast, the present invention relates to the novel discovery, and elucidation, of a pro-MS immune response; wherein the Applicants describe its involvement in the promotion of progression of MS, and describe and enable a method of reducing the pro-MS immune response.

The Examiner is respectfully reminded that when an obvious determination is based on multiple prior art references, there must be a showing of "some teaching, suggestion, or reason" to combine the references (cites); the "absence of such a

suggestion to combine is dispositive in an obviousness determination"…..…

> Although a reference need not expressly teach that the disclosure contained therein should be combined with another (cites), the showing of combinability, in whatever form, must nevertheless be "clear and particular" (cites)(emphasis added). *Winner Int'l Royalty Corp. v. Ching-Rong Wang,* 202 F.3d 1340, 1348-1349, (Fed. Cir. 2000).

In that regard, the cited combination of references lack a "clear and particular showing" of teaching, suggestion or motivation, for:

(A) a method for reducing a pro-multiple sclerosis (pro-MS) immune reponse in an individual, the method comprising administering to an individual a composition, wherein the composition comprises an affinity ligand which selectively binds to a B cell determinant, wherein the B cells targeted by the method and by the composition are nonmalignant B cells, and wherein the composition is administered in an amount effective to deplete B cells (amended claim 1 and dependent claims; amended claim 10, reciting intravenous administration, and dependent claims);

(B) a site-directed method for reducing a pro-multiple sclerosis (pro-MS) immune response in an individual, the method comprising administering to an individual a composition, wherein the composition comprises an affinity ligand which selectively binds to a B cell determinant, wherein the B cells targeted by the method and by the composition are nonmalignant B cells, wherein the composition is delivered into an access that directly supplies central nervous tissue undergoing demyelination, and wherein the composition is administered in an amount effective to deplete B cells (amended claim 6 and dependent claims); and

(C) a method for treating an individual having multiple sclerosis (MS) and a pro-MS immune response, or having a pro-MS immune response, the method comprising administering to the individual a composition, wherein the composition comprises an affinity ligand which selectively binds to a B cell determinant,

wherein the B cells targeted by the method and by the composition are nonmalignant B cells, and wherein the composition is administered in an amount to effect a reduction in inflammation underlying clinical manifestations of MS (amended claim 14, and dependent claims).

The Examiner is respectfully reminded that even if some of the features of the claimed invention are found in the prior art, such finding is insufficient by itself to establish a *prima facie* case of obviousness.

> It is not "features" but the subject matter of the invention "as a whole" that must be considered, 35 U.S.C.§103. That features, even distinguishing features, are "disclosed" in the prior art alone is insufficient. As above indicated, it is common to find elements or features somewhere in the prior art. Moreover, most if not all elements perform their ordained and expected function. The test is whether the claimed invention as a whole, in light of all the teachings of the references in their entireties, would have been obvious to one of ordinary skill in the art at the time the invention was made. 35 U.S.C. §103 (emphasis added). *Connell v. Sears, Roebuck & Co.* 220 USPQ 193,1999 (CAFC 1983).

With the above considerations and supporting legal precedence in mind, it is the Applicants' belief that the scope and content of the combination of Genain et al. and Turk et al. and Anderson et al. fails to make the claimed subject matter as a whole obvious within the meaning of §103. Accordingly, it is the Applicants' position that claims 1-17 are patentable over the cited references. Therefore, it is respectfully requested that the Examiner withdraw the rejections of claims 1-17 under §103(a).

In view of the above, favorable action on this application is respectfully requested. The Applicants invite and encourage Examiner Roark, Ph.D. to call the Applicants' attorney at (614) 818-1170 ext. 201 if there are any questions concerning this communication, or if the Examiner feels there are dis-

cussions which would expedite prosecution of this application.

Respectfully submitted,
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